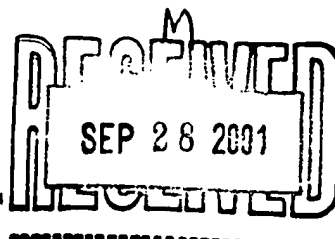


PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY



To: JANE MASSEY LICATA LICATA & TYRRELL, P.C. 66 E. MAIN STREET MARLTON, NJ 08053	Docket System <input checked="" type="checkbox"/> Status Report <input checked="" type="checkbox"/> Docket Book <input checked="" type="checkbox"/> <i>NP = 1-21-02</i>
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NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing (day/month/year)	26 SEP 2001
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Applicant's or agent's file reference RTSP-0034	IMPORTANT NOTIFICATION	
International application No. PCT/US99/29589	International filing date (day/month/year) 14 DECEMBER 1999	Priority Date (day/month/year) 21 JULY 1999
Applicant ISIS PHARMECEUTICALS, INC.		

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/MB301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer <div style="text-align: center;"> SEAN MCGARR <i>Jayne Bridges for</i> </div> Telephone No. (703) 305-0196
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RTSP-0034	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/29589	International filing date (day/month/year) 14 DECEMBER 1999	Priority date (day/month/year) 21 JULY 1999
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant ISIS PHARMECEUTICALS, INC.		

<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>4</u> sheets.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of _____ sheets.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of report with regard to novelty, inventive step or industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application

Date of submission of the demand 15 FEBRUARY 2001	Date of completion of this report 17 SEPTEMBER 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer SEAN MCGARRY
Facsimile No. (703) 305-9290	Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/29589

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed☒ the description:

pages 1-81, as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of

☒ the claims:

pages 82-83, as originally filed

pages NONE, as amended (together with any statement) under Article 19

pages NONE, filed with the demand

pages NONE, filed with the letter of

☒ the drawings:

pages NONE, as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of

☒ the sequence listing part of the description:

pages 1-12, as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).☐ the language of publication of the international application (under Rule 48.3(b)).☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in printed form.☒ filed together with the international application in computer readable form.☐ furnished subsequently to this Authority in written form.☐ furnished subsequently to this Authority in computer readable form.☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.4. ☒ The amendments have resulted in the cancellation of:☒ the description, pages NONE☒ the claims, Nos. NONE☒ the drawings, sheets 4-7 NONE5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(e)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/29589

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)	Claims	<u>1-16</u>	YES
	Claims	<u>NONE</u>	NO
Inventive Step (IS)	Claims	<u>3, 4, and 16</u>	YES
	Claims	<u>1, 2, and 5-15</u>	NO
Industrial Applicability (IA)	Claims	<u>1-16</u>	YES
	Claims	<u>none</u>	NO

2. citations and explanations (Rule 70.7)

Claims 1, 2, and 5-15 lack an inventive step under PCT Article 33(3) as being obvious over Davis et al (US 5,736,361). Davis et al disclose a nucleic acid sequence encoding MKK which is the equivalent of the Jun N-terminal kinase kinase of the instant invention. Davis et al disclose in column 3, for example that MKK can be targeted by antisense oligonucleotides and that these antisense oligonucleotides can be about 15 nucleotides in length. The modification of antisense oligonucleotide sugars bases and backbones was well known and routinely done in the art at the time the instant invention was made.

Claims 3, 4 and 16 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the specific antisense sequences of claims 3 or 4 and does not provide sufficient guidance for a method of treating disease with antisense targeted to Jun N-terminal kinase kinase.

----- NEW CITATIONS -----

none

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/29589

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): C07H 21/04; C12N 15/00; C12Q 1/68 and US Cl.: 435/6, 91.1, 91.31; 536/23.1, 24.1, 24.5